Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Clinical characteristics of diabetic nephropathy in patients with type 2 diabetic mellitus manifesting heavy proteinuria: A retrospective analysis of 220 cases

Xiaoyi Wang [a,b,1], *Jie Li* [c,1], *Lixia Huo* [d], *Yuehua Feng* [b], *Lingyan Ren* [b], *Xiner Yao* [b], *Hong Jiang* [a], *Rong Lv* [a], *Ming Zhu* [b,*], *Jianghua Chen* [a,*]

[a] *Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, China*
[b] *Department of Nephrology, The First Affiliated Hospital of Huzhou Teachers College, The First People's Hospital of Huzhou, Zhejiang Province 313000, China*
[c] *Department of Nephrology, Lishui Central Hospital, Zhejiang Province 323000, China*
[d] *Department of Central Laboratory, The First Affiliated Hospital of Huzhou Teachers College, The First People's Hospital of Huzhou, Zhejiang Province 313000, China*

ARTICLE INFO

Article history:
Received 27 June 2019
Received in revised form
18 September 2019
Accepted 30 September 2019
Available online 5 October 2019

Keywords:
Diabetic nephropathy
Non-diabetic renal disease
Type 2 diabetes mellitus
Clinical characteristics

ABSTRACT

Aims: To determine the predictability of diagnosing diabetic nephropathy (DN) versus non-diabetic renal disease (NDRD) from clinical and laboratory data in Chinese patients with type 2 diabetes mellitus (T2DM) manifesting heavy proteinuria.

Methods: We retrospectively analyzed the clinical and laboratory data of patients with T2DM manifesting heavy proteinuria who underwent renal biopsy from January 2014 to December 2017.

Results: According to renal biopsy, 220 patients were finally enrolled, including 109 cases diagnosed with DN alone (49.55%), 94 with NDRD alone (42.73%) and 17 with DN plus superimposed NDRD (7.73%). Multivariate analysis showed the significant risk factors for DN alone were age, duration of diabetes, presence of retinopathy, 24-h proteinuria, serum albumin and SBP. Presence of retinopathy achieved the highest overall diagnostic efficiency with the area under the curve of 0.852, sensitivity of 78.9% and specificity of 91.5%. The combined diagnosis with four indicators (duration of diabetes, retinopathy, SBP, and serum albumin) showed the area under the curve of 0.938, sensitivity of 88.1% and specificity of 87.2%.

Conclusions: The prevalence of DN is high in patients with T2DM manifesting heavy proteinuria. Renal biopsy should be performed in diabetics in the atypical clinical scenario.

* Corresponding authors at: Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang University and Key Laboratory of Nephropathy, Zhejiang Province, Hangzhou 313003, China (J. Chen).
E-mail addresses: zming0850@sina.com (M. Zhu), chenjianghua@zju.edu.cn (J. Chen).
[1] First author: Xiaoyi Wang and Jie Li are co-first author.

https://doi.org/10.1016/j.diabres.2019.107874
0168-8227/

1. Introduction

Diabetes is a metabolic disease characterized by persistently elevated blood sugar and can cause various clinical complications and even disability or death. In China, about 110 million people suffered from diabetes in 2017. Diabetic nephropathy (DN), one of the most common microvascular complications of diabetes, can eventually lead to end-stage renal disease (ESRD) and becomes one of the main causes of ESRD. DN accounts for 25–35% of type 2 diabetes mellitus (T2DM) [1] and significantly increases the mortality of patients with T2DM [2]. Therefore, the burden of DN exerted on social economy and public health issues cannot be ignored.

For patients with T2DM, the renal outcome of patients with non-diabetic renal disease (NDRD), a treatable or even curable disease [3,4], is better than DN. Currently, renal biopsy is the gold standard for diagnosis of pathological patterns, but this invasive test is associated with multiple risks and causes pains to the patients. Moreover, most nephrologists do not advocate renal biopsy in patients with diabetic, arguing that this procedure only confirms the presence of DN in most patients [5,6]. Thus, more accurate clinical markers should be found out to distinguish between DN and NDRD. The clinical features previously shown to predict DN include longer duration of T2DM (generally over 10 years), presence of retinopathy or neuropathy and other chronic complications, micro-albuminuria or 24-h proteinuria. Conversely, the predictors of renal involvement by NDRD in diabetic patients are short duration of DM, sudden onset of proteinuria, proteinuria in the absence of retinopathy or neuropathy, a large number of hematuria, and acute renal failure. However, the onset of DN is concealed. The early clinical manifestation is microalbuminuria, but no obvious symptoms. Though most patients are in stage IV upon diagnosis, there are few reports on the clinical features of this stage.

The present study was aimed to determine the predictors of DN and NDRD in China patients with T2DM manifesting heavy proteinuria and referred to our centers. For this purpose, we retrospectively evaluated the relationship between clinical features and laboratory data in T2DM with heavy proteinuria who underwent renal biopsy in our centers.

2. Methods

2.1. Patients

The study was approved by the Ethics Committees of Medical Center of the First Affiliated Hospital of Huzhou Teachers College, the First Affiliated Hospital of Zhejiang University and Lishui Central Hospital. All patients provided written informed consent.

The medical records of T2DM patients who underwent renal biopsy in these three Hospitals from January 2014 to December 2017 were reviewed retrospectively. The inclusion criteria were as follows: age between 20 and 80 years; urinary protein excretion $\geq$3 g/24 h; serum creatinine <442 umol/L and voluntary admission for renal biopsy. Exclusion criteria were as follows: a clinically confirmed diagnosis of lupus nephritis and Henoch-Schönlein purpura nephritis; familial hereditary nephropathies, such as autosomal dominant polycystic kidney disease; an uncertain pathological diagnosis. The pathology (histopathological findings) was diagnosed by at least two pathologists and two other nephrologists.

2.2. Clinical and laboratory indexes

The following clinical data were collected at the time of renal biopsy from each patient: age, gender, duration of T2DM prior to biopsy (since diagnosis of T2DM), history of proteinuria, duration of hypertension, diabetic retinopathy, systolic pressure, and diastolic pressure. Laboratory indexes tested at the time of biopsy were as follows: urine erythrocyte count, 24-h proteinuria, serum albumin, blood urea nitrogen, serum creatinine (umol/l), estimated glomerular filtration rate (eGFR), hemoglobin (Hb), total cholesterol, triglycerides, and low-density lipoprotein. Diabetic retinopathy was diagnosed by an ophthalmologist through direct ophthalmoscopy.

2.3. Statistical analysis

Analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA). The descriptive statistics were presented as mean ± standard deviation (SD) or median (quartile) for measurement data and as percentage for enumeration data. The continuous variables were compared among groups by independent *t*-test or analysis of variance (ANOVA) for the normally distributed data or by the Mann-Whitney *U* test for the unnormally distributed data. The categorical variables were compared using the chi-squared test. The variables at $P < 0.1$ were introduced into stepwise multivariate logistic regression to screen out the DN diagnostic parameters. Multivariate logistic regression of receiver operating characteristic curve (AUC) was conducted ($P < 0.05$) to calculate the area under the curve, sensitivity and specificity and to identify diagnostic efficiency.

3. Results

3.1. Clinical characteristics

A total of 442 T2DM patients underwent renal biopsy from January 1, 2014 to December 31, 2017, but 220 (49.77%) patients were finally enrolled, including 109 cases diagnosed as DN alone, 94 cases as NDRD alone and 17 cases as DN plus superimposed NDRD. Key clinical and laboratory data at time of renal biopsy of the cohort were summarized in Table 1. The mean age of the cohort at biopsy was 54.70 ± 10.54 years, although patients with DN alone were slightly younger than patients with NDRD. The male:female ratio was 2.2:1.0.

Comparison of clinical features among groups demonstrated significant difference in duration of diabetes (since diagnosis of T2DM), diabetic retinopathy, blood pressure, urine erythrocyte count, proteinuria (g/24 h), serum albumin, blood urea nitrogen, serum creatinine, eGFR, hemoglobin and low density lipoprotein ($P < 0.05$; Table1).

Table 1 – Key clinical and laboratory data at time of kidney biopsy in patients with T2DM.

	All (n = 220)	DN Alone (n = 109)	NDRD Alone (n = 94)	DN Plus NDRD (n = 17)	*p*-Value
Age (yr)	54.70 ± 10.55	53.08 ± 9.86	56.34 ± 11.11	55.94 ± 10.66	0.079
Sex (male, %)	151 (68.6%)	76 (69.7%)	63 (67%)	12 (70.6%)	0.204
Duration of T2DM (yr)	5.0 (1.0,10.0)	10.0 (5.0,11.0)	1.0 (0.0,5.3)[a]	5.0 (2.0,10.0)[c]	<0.001
History of Proteinuria (yr)	0.25(0.08,1.00)	0.25(0.08,1.00)	0.17(0.08,0.80)	0.17(0.03,0.83)	0.523
Duration of Hypertension (yr)	0.17(0,0.83)	0.08(0.01,0.83)	0.25(0,0.83)	0.08(0.04,0.58)	0.991
Diabetic retinopathy (yes,%)	101 (45.9%)	86 (78.9%)	8 (8.5%)[a]	7 (41.2%)[b,c]	<0.001
SBP (mmHg)	152.1 ± 23.6	158.5 ± 23.0	145.2 ± 22.5[a]	148.6 ± 23.0	<0.001
DBP (mmHg)	86.6 ± 13.9	88.6 ± 13.2	84.6 ± 12.3	84.5 ± 23.3	0.042
Urine erythrocyte count (n/ul)	25.0 (8.0,63.9)	21.6 (3.0,47.7)	39.8 (13.8,86.0)[a]	12.0 (9.0,25.5)[c]	<0.001
Proteinuria (g/24 h)	5.1 (3.8,6.9)	5.2 (3.9,7.1)	4.6 (3.7,6.3)	7.1 (4.5,10.0)[c]	0.012
Serum albumin (g/l)	27.9 ± 7.6	30.4 ± 6.7	25.6 ± 7.5[a]	25.0 ± 8.5[b]	<0.001
Blood urea nitrogen (mmol/l)	7.4 (5.5,10.4)	8.0 (6.0,12.0)	7.0 (5.0,9.0)[a]	8.0 (5.0,9.5)	0.014
Serum creatinine (umol/l)	101.5 (76.0,149.0)	121.0 (82.0,169.0)	89.5 (67.8,130.5)[a]	110.0 (92.5,143.5)	<0.001
eGFR (ml/min per 1.73 m^2)	69.5 ± 30.7	62.0 ± 25.2	78.4 ± 34.0[a]	68.5 ± 32.9	<0.001
Hemoglobin	118.9 ± 22.8	113.3 ± 22.0	126.9 ± 22.0[a]	110.9 ± 19.2[c]	<0.001
Total cholesterol (mmol/l)	6.1 (4.8,7.7)	5.6 (4.5,7.5)	6.3 (4.9,8.1)	6.4 (4.9,7.0)	0.102
Triglycerides (mmol/l)	2.0 (1.4,2.8)	2.0 (1.4,2.7)	2.2 (1.5,3.0)	2.0 (1.3,2.7)	0.537
Low density lipoprotein (mmol/l)	3.4 (2.4,4.5)	3.2 (2.4,4.0)	3.9 (2.5,5.2)[a]	3.5 (2.0,3.9)	0.038

Categorical variables are expressed as *n* (%); continuous variables are expressed as median (interquartile range). NDRD, nondiabetic renal disease.

[a] P < 0.05: DN alone versus NDRD alone.

[b] P < 0.05: DN alone versus DN plus NDRD.

[c] P < 0.05: NDRD alone versus DN plus NDRD.

3.2. *Risk factors for prediction of DN*

Univariate analysis showed the DN patients versus the NDRD patients had significantly longer duration of diabetes, higher blood pressure, serum albumin, blood urea nitrogen and serum creatinine, lower levels of urine erythrocyte, eGFR, hemoglobin and low density lipoprotein, and more common diabetic retinopathy. Some other characteristics were also different between the two groups (Table 2).

Multivariate logistic regression of the significant variables found in the univariate analysis was conducted to determine the risk factors associated with DN alone or with NDRD alone (Table 3). Significant risk factors for DN alone were age (OR 0.178; 95%CI = 0.056–0.569; p = 0.004), duration of T2DM (OR 1.270; 95%CI = 1.133–1.423; p < 0.001), presence of retinopathy (the most important factor; OR 60.359; 95%CI = 17.134–212.633; p < 0.001), 24-h proteinuria (OR 1.243; 95%CI = 1.006–1.537; p = 0.004), serum albumin (OR 1.112; 95%CI = 1.028–1.203; p = 0.008), and SBP (OR 1.048; 95%CI = 1.021–1.074; p < 0.001). The probability of DN in patients with retinopathy versus without retinopathy was 60.359 times. The likelihood to have DN was 1.270 times higher by every additional year of diabetes history. Age above 60 was a protective factor of DN. The probability of having diabetic versus non-diabetic nephropathy in patients older than 60 years was 0.178 times.

3.3. *Diagnostic performance of clinical indicators for predicting DN development*

We evaluated the sensitivity and specificity of those factors in predicting DN alone or NDRD alone in ROC analysis (Table 4). For the DN alone, presence of retinopathy, duration of T2DM ≥ 7.5 years, serum albumin ≥ 28.325 g/l, and SBP ≥ 150.50 mmHg (cut-off value of ROC analysis) showed the largest AUC. When retinopathy, duration of T2DM, serum albumin, and SBP were combined, the AUC, specificity and sensitivity were higher than those diagnosed alone.

4. Discussion

About 30–40% of patients with history of at least 10 years of diabetes show significant DN. However, increasing evidence indicates many newly-diagnosed cases of DN are developing NDRD or DN superimposed NDRD. Correct classification of these cases is critical in predicting the disease progression and in developing appropriate treatments timely.

In this study, DN was identified in 57.27% of biopsies: 109 patients with DN alone and 17 with DN plus NDRD, which are most similar to another report [7]. The proportion of DN in patients with diabetic renal disease reportedly ranges from 8% to 94% [7–11]. Moreover, NDRD was identified in 50.46% of biopsies: 94 patients with NDRD alone and 17 with DN plus NDRD, which are most similar to another report [12]. The prevalence of NDRD in diabetic patients with kidney involvement varies widely from 3% to 82.9% [8,12,13]. The large variation in the prevalence of DN or NDRD may be due to differences in renal biopsy criteria, inclusion criteria, or geographical and ethnic conditions. In each group, the prevalence of men versus women was higher, but no significant difference was found among the three groups, similar to other research results.

This study included a large sample of patients with T2DM undergoing renal biopsy and objectively evaluated the clinical characteristics of DN patients in our centers. Results show longer duration of diabetes, presence of retinopathy (the most important factor), higher serum albumin and SBP are

Table 2 – Univariate analysis of DN alone and NDRD alone.

	NDRD (n = 94)	DN (n = 109)	t/χ2	p
Age (yr)				
<60	53	83	8.916	0.003
≥60	41	26		
Sex (male, %)				
Male	63	76	0.171	0.679
Female	31	33		
Duration of T2DM (yr)	1.14(0.08,5.25)	9.00(4.00,10.00)	7.010	<0.001
Duration of Proteinuria (yr)	0.17(0.08,0.80)	0.25(0.08,1.00)	0.197	0.844
Duration of Hypertension (yr)	0.25(0,0.83)	0.08(0.01,0.83)	−0.098	0.922
Diabetic retinopathy (%)				
Yes	86	23	100.577	<0.001
No	8	86		
SBP (mmHg)	145.20 ± 22.53	158.52 ± 22.97	−4.156	<0.001
DBP (mmHg)	84.61 ± 12.25	88.57 ± 13.20	−2.204	0.029
Urine erythrocyte count (n/ul)				
<3	6	21	7.265	0.007
≥3	88	88		
Proteinuria (g/24 h)	4.56(3.70,6.30)	5.22(3.93,7.13)	1.735	0.083
Serum albumin (g/l)	25.55 ± 7.49	30.35 ± 6.66	−4.826	<0.001
Blood urea nitrogen (mmol/l)	6.80(5.01,8.88)	7.72(6.10,11.98)	2.944	0.003
Serum creatinine (umol/l)	89.50(67.75,130.50)	121.00(82.00,169.00)	3.627	<0.001
eGFR (ml/min per 1.73 m^2)	77.62(51.89,102.00)	65.34(41.90,79.33)	−3.744	<0.001
Hemoglobin	126.94 ± 21.99	113.27 ± 21.99	4.416	<0.001
Total cholesterol l(mmol/l)	6.34(4.90,8.11)	5.58(4.48,7.46)	−2.099	0.036
Triglycerides (mmol/l)	2.17(1.45,3.00)	2.03(1.43,2.67)	−1.077	0.281
Low density lipoprotein (mmol/l)	3.88(2.47,5.24)	3.22(2.35,4.03)	−2.461	0.014

Table 3 – Multivariate logistic regression analysis of DN alone and NDRD alone.

Indicator	β-Estimate	Standard error	*p*-Value	Odds ratio	95% confidence interval
Age (≥60)	−1.724	0.592	0.004	0.178	0.056–0.569
Duration of T2DM (yr)	0.239	0.058	<0.001	1.270	1.133–1.423
Diabetic retinopathy (yes vs. no)	4.100	0.642	<0.001	60.359	17.134–212.633
Proteinuria (g/24 h)	0.218	0.108	0.044	1.243	1.006–1.537
Serum albumin (g/l)	0.106	0.040	0.008	1.112	1.028–1.203
SBP (mmHg)	0.046	0.013	<0.001	1.048	1.021–1.074

significant independent predictors for development of DN based on the ROC curves. A meta-analysis reported the absence of diabetic retinopathy (DR), shorter history of diabetes, and lower HbA1c and systolic pressure were relatively good predictors in differentiating NDRD from DN [14]. Our results are consistent with many reports that serum albumin is also an important clinical indicator for identification of DN, which cannot be ignored.

DR, one of the microvascular complications of DM, may have the same pathogenetic pathways as DN. Retinopathy, when it coexists with nephropathy, is thought to be a window of renal complication. DR may be an indicator of DN, as confirmed in many studies. DR and albuminuria should be considered to determine renal function decline in T2DM [15]. DR may predict the renal prognosis of patients with T2DM and DN [16]. Moreover, proliferative diabetic retinopathy is associated with microalbuminuria and DR is related with overt nephropathy in Korean DM patients [17]. In our study, 90% of the T2DM patients with DR were DN and 76% of patients without DR were NDRD, suggesting non-DR was a rather good indicator for NDRD. Notably, the absence of DR was predictive of NDRD development, but not an exclusion criterion for DN.

Short duration of DM is repeatedly a strong clinical predictor of NDRD in most studies. In our study, duration of diabetes is an indicator of DN alone in T2DM. Duration of DM ≥7.5 years emerged as the best predictor of DN alone (56.9% sensitivity and 85.1% specificity). Reportedly, duration of DM ≥12 years was found as the best predictor (57.5% sensitivity and 73.3% specificity) [18] and DM history ⩽5 years (71.71% sensitivity and 78.13% specificity) was believed to be a significant and independent risk factor for the development of NDRD [19]. In DN, the transition from micro- to macroalbuminuria and even renal failure takes quite long time.

Table 4 – Sensitivity and specificity of significant variables in predicting DN alone and NDRD alone.

Indicator	AUC	Sensitivity (%)	Specificity (%)	*p*-Value	95% confidence interval
Age (≥60)	0.599	76.1	43.6	0.015	0.520–0.677
Duration of T2DM (yr)	0.785	56.9	85.1	<0.001	0.721–0.849
Diabetic retinopathy (yes vs. no)	0.852	78.9	91.5	<0.001	0.796–0.908
Proteinuria (g/24 h)	0.571	58.7	55.3	0.083	0.492–0.650
Serum albumin (g/l)	0.677	59.6	62.8	<0.001	0.604–0.751
SBP (mmHg)	0.673	67.0	63.8	<0.001	0.599–0.747
Duration of T2DM + Plasma albumins + Diabetic retinopathy + SBP	0.938	88.1	87.2	<0.001	0.906–0.971

DN is one of the chronic complications of diabetes. Clinical abnormalities are often detected 5–10 years after onset or diagnosis of DM. However, microalbuminuria should be examined in patients with T2DM after diagnosis, as some patients may have hyperglycemia but do not know it, and the kidney may be damaged when symptoms appear. Therefore, the duration of DM is used as an indicator for diagnosing DN, and the range of its predicted value is larger. However, T2DM may have developed long before the diagnosis. Therefore, the known diabetes duration does not accurately predict the presence or severity of DN.

Hypertension is common in patients with T2DM. The DN group manifested hypertension more often and more severely than the NDRD group in our study. Hypertension is an important factor in DN and is associated with the risk of macrovascular and microvascular complications in T2DM patients [20]. A retrospective cohort study reveals that visit-to-visit SBP variability is a significant predictor in the development and progression of DN [21]. Maximum morning home SBP is an indicator of DN development [22]. Masked hypertension may be a predictor of progression to macroalbuminuria among patients with T2DM [23]. The BP reduction may play a role in DN treatment [24]. Diabetes and hypertension can synergistically enhance glomerular hypertrophy across all layers of the human renal cortex [25]. The sensitivity and specificity of the presence of hypertension in predicting DN were 67.0% and 63.8%, which are different from another study (85.76% and 47.13%) and may be related to the patients enrolled [26]. However, we all recommend patients with T2DM should regularly measure and there control blood pressure timely, which is beneficial to delaying the progression of DN.

Hypoalbuminemia is frequently found in most DN patients. Our study shows serum albumin is a factor in predicting DN, but this view is controversial. The serum albumin level in DN patients is significantly correlated with proteinuria, renal function and glomerular lesions; the severity of hypoalbuminemia is significantly associated with an adverse renal outcome [27]. After accounting for the competing risk of death, DN along with lower hemoglobin, lower eGFR and severe proteinuria are independent predictors for ESRD [28]. In addition, proteinuria, hypoalbuminemia, anemia, and a change in SBP are risk factors for progression of renal disease in DN patients [29]. These findings suggest the serum albumin levels may be an important clinical predictor of DN and NDRD.

Our study has several obvious limitations. This retrospective study cannot avoid information bias. Duration of diabetes (since diagnosis of T2DM), history of proteinuria and duration of hypertension were sometimes according to the patient's own report, which maybe led to recall bias. Similarly, hemoglobin A1c values were missing for most patients and thus cannot be included in our analyses.

In conclusion, longer duration of diabetes (≥7.5 years), presence of retinopathy, higher SBP, and higher serum albumin are independent indicators associated with DN. Renal biopsy should be recommended for T2DM patients with atypical nephropathy, because a considerable number of such patients may have NDRD. Large-scale, multicenter, randomized and prospective studies are needed to differentiate DN from the NDRD superimposed on DN, which should contribute to specific treatment, improve renal outcomes and reduce the prevalence of ESRD in T2DM patients.

Acknowledgements

The authors thank the physicians and patients who participated in the study.

Funding

This work was supported by Zhejiang Basic Public Welfare Research Project [Grant No. LGF18H050002]; Zhejiang Medical and Health Science and Technology Project [Grant No. 2016KYA172, 2017KYB639, 2017KY643] and Huzhou Municipal Science and Technology Bureau Public Welfare Application Research Project [Grant No. 2014GZ09, 2016GY27].

Declaration of Competing Interest

The authors have declared that no conflict of interest exists.

REFERENCES

[1] Eppens MC, Craig ME, Cusumano J, et al. Prevalence of diabetes complications in adolescents with type 2 compared with type 1 diabetes. Diabetes Care 2006;29(6):1300–6.
[2] Afkarian M, Sachs MC, Kestenbaum B, et al. Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol 2013;24(2):302–8.
[3] Chang TI, Park JT, Kim JK, et al. Renal outcomes in patients with type 2 diabetes with or without coexisting non-diabetic renal disease. Diabetes Res Clin Pr 2011;92(2):198–204.

[4] Stanton RC. Clinical challenges in diagnosis and management of diabetic kidney disease. Am J Kidney Dis 2014;63(2 Suppl 2):S3–S21.
[5] Oh SW, Kim S, Na KY, et al. Clinical implications of pathologic diagnosis and classification for diabetic nephropathy. Diabetes Res Clin Pr. 2012;97(3):418–24.
[6] Zhang PP, Ge YC, Li SJ, et al. Renal biopsy in type 2 diabetes: timing of complications and evaluating of safety in Chinese patients. Nephrology 2011;16(1):100–5.
[7] Liu D, Huang T, Chen N, et al. The modern spectrum of biopsy-proven renal disease in Chinese diabetic patients-a retrospective descriptive study. PeerJ 2018;6:e4522.
[8] Zhuo L, Ren W, Li W, et al. Evaluation of renal biopsies in type 2 diabetic patients with kidney disease: a clinicopathological study of 216 cases. Int Urol Nephrol 2013;45(1):173–9.
[9] Schwartz MM, Lewis EJ, Leonard-Martin T, et al. Renal pathology patterns in type II diabetes mellitus: relationship with retinopathy. The Collaborative Study Group. Nephrol Dial Transplant 1998;13(10):2547–52.
[10] Lin YL, Peng SJ, Ferng SH, et al. Clinical indicators which necessitate renal biopsy in type 2 diabetes mellitus patients with renal disease. Int J Clin Pract 2009;63(8):1167–76.
[11] Pham TT, Sim JJ, Kujubu DA, et al. Prevalence of nondiabetic renal disease in diabetic patients. Am J Nephrol 2007;27 (3):322–8.
[12] Horvatic I, Tisljar M, Kacinari P, et al. Non-diabetic renal disease in Croatian patients with type 2 diabetes mellitus. Diabetes Res Clin Pr 2014;104(3):443–50.
[13] Mou S, Wang Q, Liu J, et al. Prevalence of non-diabetic renal disease in patients with type 2 diabetes. Diabetes Res Clin Pr 2010;87(3):354–9.
[14] Fiorentino M, Bolignano D, Tesar V, et al. Renal biopsy in patients with diabetes: a pooled meta-analysis of 48 studies. Nephrol Dial Transplant 2017;32(1):97–110.
[15] Moriya T, Matsubara M, Kishihara E, et al. Type 2 diabetic patients with diabetic retinopathy and concomitant microalbuminuria showed typical diabetic glomerulosclerosis and progressive renal dysfunction. J Diabetes Complicat 2016;30(6):1111–6.
[16] Zhang JL, Wang YT, Li L, et al. Diabetic retinopathy may predict the renal outcomes of patients with diabetic nephropathy. Ren Fail 2018;40(1):243–51.
[17] Lee WJ, Sobrin L, Lee MJ, et al. The relationship between diabetic retinopathy and diabetic nephropathy in a population-based study in Korea (KNHANES V-2, 3). Invest Ophth Vis Sci 2014;55(10):6547–53.
[18] Sharma SG, Bomback AS, Radhakrishnan J, et al. The modern spectrum of renal biopsy findings in patients with diabetes. Clin J Am Soc Nephro. 2013;8(10):1718–24.
[19] Dong ZY, Wang YD, Qiu Q, et al. Clinical predictors differentiating non-diabetic renal diseases from diabetic nephropathy in a large population of type 2 diabetes patients. Diabetes Res Clin Pr 2016;121:112–8.
[20] Viigimaa M, Sachinidis A, Toumpourleka M, et al. Macrovascular complications of type 2 diabetes mellitus. Curr Vasc Pharmacol 2019.
[21] Takao T, Matsuyama Y, Yanagisawa H, et al. Visit-to-visit variability in systolic blood pressure predicts development and progression of diabetic nephropathy, but not retinopathy, in patients with type 2 diabetes. J Diabetes Complicat. 2014;28 (2):185–90.
[22] Okamura T, Ushigome E, Kitagawa N, et al. Maximum morning home systolic blood pressure is an indicator of the development of diabetic nephropathy: The KAMOGAWA-HBP study. J Diabetes Investig 2019.
[23] Ushigome E, Oyabu C, Tanaka T, et al. Impact of masked hypertension on diabetic nephropathy in patients with type II diabetes: a KAMOGAWA-HBP study. J Am Soc Hypertens 2018;12(5):364–71. e361.
[24] Chong YB, Keng TC, Tan LP, et al. Clinical predictors of non-diabetic renal disease and role of renal biopsy in diabetic patients with renal involvement: a single centre review. Ren Fail 2012;34(3):323–8.
[25] Sasaki T, Tsuboi N, Okabayashi Y, et al. Synergistic impact of diabetes and hypertension on the progression and distribution of glomerular histopathological lesions. Am J Hypertens 2019.
[26] Wang J, Han Q, Zhao L, et al. Identification of clinical predictors of diabetic nephropathy and non-diabetic renal disease in Chinese patients with type 2 diabetes, with reference to disease course and outcome. Acta Diabetol 2019.
[27] Zhang J, Zhang R, Wang Y, et al. The level of serum albumin is associated with renal prognosis in patients with diabetic nephropathy. J Diabetes Res 2019;2019:7825804.
[28] Chou YH, Lin WC, Chen YM. Clinical outcomes in patients with biopsy-proved diabetic nephropathy compared to isolated lupus or crescentic glomerulonephritis. Diabetes Res Clin Pr 2019;148:144–51.
[29] Unsal A, Koc Y, Basturk T, et al. Risk factors for progression of renal disease in patient with diabetic nephropathy. Eur Rev Med Pharmaco 2012;16(7):878–83.